

**ENDOLUMINAL DEVICE EXHIBITING IMPROVED ENDOTHELIALIZATION AND
METHOD OF MANUFACTURE THEREOF**

Cross-Reference to Related Application

This application is a divisional application and corresponds to and claims priority of
5 pending U.S. utility patent application, Serial No. 09/433,929, filed November 19, 1999. ^{new US Patent}
No. 6348960

Background of the Invention

10 The present invention relates generally to implantable endoluminal medical devices
which contact biological fluids and tissues on at least one surface of the medical device. More
particularly, the present invention relates to endoluminal stents which are implanted into
anatomical passageways using minimally invasive techniques. Endoluminal stents are
15 frequently used post-angioplasty in order to provide a structural support for a blood vessel and
reduce the incidence of restenosis following percutaneous balloon angioplasty. A principal
example of the present invention are endovascular stents which are introduced to a site of disease
or trauma within the body's vasculature from an introductory location remote from the disease or
trauma site using an introductory catheter, passed through the vasculature communicating
20 between the remote introductory location and the disease or trauma site, and released from the
introductory catheter at the disease or trauma site to maintain patency of the blood vessel at
the site of disease or trauma.

While the use of endoluminal stents has successfully decreased the rate of restenosis in
20 angioplasty patients, it has been found that a significant restenosis rate continues to exist even

with the use of endoluminal stents. It is generally believed that the post-stenting restenosis rate is due, in major part, to a failure of the endothelial layer to regrow over the stent and the incidence of smooth muscle cell-related neo-intimal growth on the luminal surfaces of the stent. Injury to the endothelium, the natural nonthrombogenic lining of the arterial lumen, is a significant factor contributing to restenosis at the situs of a stent. Endothelial loss exposes thrombogenic arterial wall proteins, which, along with the generally thrombogenic nature of many prosthetic materials, such as stainless steel, titanium, tantalum, Nitinol, etc. customarily used in manufacturing stents, initiates platelet deposition and activation of the coagulation cascade, which results in thrombus formation, ranging from partial covering of the luminal surface of the stent to an occlusive thrombus. Additionally, endothelial loss at the site of the stent has been implicated in the development of neointimal hyperplasia at the stent situs. Accordingly, rapid re-endothelialization of the arterial wall with concomitant endothelialization of the body fluid or blood contacting surfaces of the implanted device, is considered critical for maintaining vasculature patency and preventing low-flow thrombosis.

At present, most endoluminal stents are manufactured of stainless steel, which is known to be thrombogenic. In order to reduce the thrombogenicity of the stainless steel and to maintain sufficient dimensional profiles for catheter delivery, most stents minimize the metal surface area which contacts blood, in order to minimize thrombus formation after implantation. Thus, in order to reduce the thrombogenic response to stent implantation, as well as reduce the formation of neointimal hyperplasia, it would be advantageous to increase the rate at which endothelial cells from endothelium proximal and distal to the stent situs, migrate onto and the endothelial

coverage of the luminal surface of the stent which is in contact with blood flow through the vasculature.

5 The surface of a solid, homogeneous material can be conceptualized as having unsaturated inter-atomic and intermolecular bonds forming a reactive plane ready to interact with the environment. In practice, a perfectly clean surface is unattainable because of immediate adsorption of airborne species, upon exposure to ambient air, of O, O₂, CO₂, SO₂, NO, hydrocarbons and other more complex reactive molecules. Reaction with oxygen implies the formation of oxides on a metal surface, a self-limiting process, known as passivation. An oxidized surface is also reactive with air, by adsorbing simple, organic airborne compounds. Assuming the existence of bulk material of homogeneous subsurface and surface composition, oxygen and hydrocarbons may adsorb homogeneously. Therefore, further exposure to another environment, such as the vascular compartment, may be followed by a uniform biological response.

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20 Current metallic vascular devices, such as stents, are made from bulk metals made by conventional methods, and stent precursors, such as hypotubes, are made with many steps each of which introduce processing aides to the metals. For example, olefins trapped by cold drawing and transformed into carbides or elemental carbon deposit by heat treatment, typically yield large carbon rich areas in 316L stainless steel tubing manufactured by cold drawing process. The conventional stents have marked surface and subsurface heterogeneity resulting from manufacturing processes (friction material transfer from tooling, inclusion of lubricants, chemical segregation from heat treatments). This results in formation of surface and subsurface inclusions with chemical composition and, therefore, reactivity different from the bulk material.

Oxidation, organic contamination, water and electrolytic interaction, protein adsorption and cellular interaction may, therefore, be altered on the surface of such inclusion spots.

Unpredictable distribution of inclusions such as those mentioned above provide an unpredictable and uncontrolled heterogeneous surface available for interaction with plasma proteins and cells.

5 Specifically, these inclusions interrupt the regular distribution pattern of surface free energy and electrostatic charges on the metal surface that determine the nature and extent of plasma protein interaction. Plasma proteins deposit nonspecifically on surfaces according to their relative affinity for polar or non-polar areas and their concentration in blood. A replacement process known as the Vroman effect, Vroman L. The importance of surfaces in contact phase reactions,
10 *Seminars of Thrombosis and Hemostasis* 1987;13(1):79-85, determines a time-dependent sequential replacement of predominant proteins at an artificial surface, starting with albumin, following with IgG, fibrinogen and ending with high molecular weight kininogen. Despite this variability, some of the adsorbed proteins have receptors available for cell attachment and therefore constitute adhesive sites. Examples are: fibrinogen glycoprotein receptor IIb/IIIa for
15 platelets and fibronectin RGD sequence for many blood activated cells. Since the coverage of an artificial surface with endothelial cells is a favorable end-point in the healing process, to favor endothelialization is desirable in implantable vascular device manufacture.

Normally, endothelial cells (EC) migrate and proliferate to cover denuded areas until confluence is achieved. Migration, quantitatively more important than proliferation, proceeds
20 under normal blood flow roughly at a rate of 25 $\mu\text{m/hr}$ or 2.5 times the diameter of an EC, which is nominally 10 μm . EC migrate by a rolling motion of the cell membrane, coordinated by a complex system of intracellular filaments attached to clusters of cell membrane attachment,

integrin receptors, specifically focal contact points. The integrins within the focal contact sites are expressed according to complex signaling mechanisms and eventually couple to specific amino acid sequences in substrate adhesion molecules (such as RGD, mentioned above). An EC has roughly 16-22% of its cell surface represented by integrin clusters Davies P.F., Robotewskyi A., Griem M.L. Endothelial cell adhesion in real time. *J.Clin.Invest.* 1993;91:2640-2652, Davies, P.F., Robotewski, A., Griem, M.L. , Qualitative studies of endothelial cell adhesion, *J.Clin.Invest.* 1994;93:2031-2038. This is a dynamic process, which implies more than 50% remodeling in 30 minutes. The focal adhesion contacts vary in size and distribution, but 80% of them measure less than $6\mu\text{m}^2$, with the majority of them being about $1\mu\text{m}^2$, and tend to elongate in the direction of flow and concentrate at leading edges of the cell. Although the process of recognition and signaling to determine specific attachment receptor response to attachment sites is incompletely understood, regular availability of attachment sites, more likely than not, would favorably influence attachment and migration. Irregular or unpredictable distribution of attachment sites, that might occur as a result of various inclusions, with spacing equal or smaller to one whole cell length, is likely to determine alternating hostile and favorable attachment conditions along the path of a migrating cell. These conditions may vary from optimal attachment force and migration speed to insufficient holding strength to sustain attachment, resulting in cell slough under arterial flow conditions. Due to present manufacturing processes, current implantable vascular devices exhibit such variability in surface composition as determined by surface sensitive techniques such as atomic force microscopy, X-ray photoelectron spectroscopy and time of flight secondary ion-mass spectroscopy.

There have been numerous attempts to increase endothelialization of implanted stents, including covering the stent with a polymeric material (U.S. Patent No. 5,897,911), imparting a diamond-like carbon coating onto the stent (U.S. Patent No. 5,725,573), covalently binding hydrophobic moieties to a heparin molecule (U.S. Patent No. 5,955,588), coating a stent with a layer of blue to black zirconium oxide or zirconium nitride (U.S. Patent No. 5,649,951), coating a stent with a layer of turbostratic carbon (U.S. Patent No. 5,387,247), coating the tissue-contacting surface of a stent with a thin layer of a Group VB metal (U.S. Patent No. 5,607,463), imparting a porous coating of titanium or of a titanium alloy, such as Ti-Nb-Zr alloy, onto the surface of a stent (U.S. Patent No. 5,690,670), coating the stent, under ultrasonic conditions, with a synthetic or biological, active or inactive agent, such as heparin, endothelium derived growth factor, vascular growth factors, silicone, polyurethane, or polytetrafluoroethylene, U.S. Patent No. 5,891,507), coating a stent with a silane compound with vinyl functionality, then forming a graft polymer by polymerization with the vinyl groups of the silane compound (U.S. Patent No. 5,782,908), grafting monomers, oligomers or polymers onto the surface of a stent using infrared radiation, microwave radiation or high voltage polymerization to impart the property of the monomer, oligomer or polymer to the stent (U.S. Patent No. 5,932,299). Thus, the problems of thrombogenicity and re-endothelialization associated with stents have been addressed by the art in various manners which cover the stent with either a biologically active or an inactive covering which is less thrombogenic than the stent material and/or which has an increase capacity for promoting re-endothelialization of the stent situs. These solutions, however, all require the use of existing stents as substrates for surface derivatization or modification, and each of the solutions result in a biased or laminate structure built upon the stent substrate. These prior art

coated stents are susceptible to delamination and/or cracking of the coating when mechanical stresses of transluminal catheter delivery and/or radial expansion *in vivo*. Moreover, because these prior art stents employ coatings applied to stents fabricated in accordance with conventional stent formation techniques, *e.g.*, cold-forming metals, the underlying stent substrate is characterized by uncontrolled heterogeneities on the surface thereof. Thus, coatings merely are laid upon the heterogeneous stent surface, and inherently conform to the heterogeneities in the stent surface and mirror these heterogeneities at the blood contact surface of the resulting coating. This is conceptually similar to adding a coat of fresh paint over an old coating of blistered paint, the fresh coating will conform to the blistering and eventually, itself, blister and delaminate from the underlying substrate.

The current invention entails creating materials specifically designed for manufacture of stents and other intravascular devices. Manufacture of stents and other intravascular devices is controlled to attain a regular, homogeneous atomic and molecular pattern of distribution along their surface. This avoids the marked variations in surface composition, would create a predictable oxidation and organic adsorption pattern and would have a predictable interaction with water, electrolytes, proteins and cells. Particularly, EC migration would be supported by a homogeneous distribution of binding domains which serve as natural or implanted cell attachment sites, in order to promote unimpeded migration and attachment. Based on observed EC attachment mechanisms such binding domains should have a repeating pattern along the blood contact surface of no less than 1 μm radius and 2 μm border to border spacing between binding domains. Ideally, the inter-binding domain spacing is less than the nominal diameter of

an endothelial cell in order to ensure that at any given time, a portion of an endothelial cell is in proximity to a binding domain.

Summary of the Invention

In accordance with the present invention, there is provided an implantable endoluminal device which is fabricated from materials which present a blood contact surface which is substantially homogeneous in material constitution. More particularly, the present invention provides an endoluminal stent which is made of a material having controlled heterogeneities along the blood flow surface of the stent. The heterogeneities which are controlled in the present invention include: grain size, grain phase, grain material composition, stent-material composition, and surface topography at the blood flow surface of the stent. Additionally, the present invention provides methods of making an endoluminal stent having controlled heterogeneities in the stent material along the blood flow surface of the stent.

Brief Description of the Figures

Figure 1 is a diagrammatic representation of controlled heterogeneities in the inventive stent.

Figure 2 is a micrograph of uncontrolled heterogeneities present in prior art stent material.

Detailed Description of the Preferred Embodiments

Blood protein interaction with surfaces of endoluminal devices appears to be an initial step in a chain of events leading to tissue incorporation of the endovascular device. The present invention is based, in part, upon the relationship between surface energy of the material used to make the endoluminal device and protein adsorption at the surface of the endoluminal device. The present inventors have found that a relationship exists between surface free energy and protein adsorption on metals commonly used in fabrication of endoluminal devices. In addition, specific electrostatic forces resident on the surface of metal endoluminal stents have been found to influence blood interactions with the stent surface and the vascular wall.

In accordance with the present invention there is provided a stent which is fabricated of a material having substantially homogeneous surface properties, specifically surface energy and electrostatic charge, across the blood contact surface of the stent. Current manufacturing methods for fabricating endoluminal stents fail to achieve the desired material properties of the present invention. As discussed above, stents are fabricated from bulk metals which are processed in a manner which introduces processing aides to the metal. Presently, stents are made from hypotubes formed from the bulk metals, by machining a series of slots or patterns into the hypotube to accommodate radial expansion into a stainless steel metal tube, or by weaving wires into a mesh pattern. According to the present invention, a stent with a substantially homogeneous metal constitution, exhibiting substantially homogeneous surface properties is made by imparting a stent pattern, suitable for making either a balloon expandable or self expanding stent, onto a substrate and depositing stent-forming metal onto the stent pattern by a deposition methodology which yields a metal having controlled heterogeneities. Suitable

deposition methodologies, as are known in the microelectronic and vacuum coating fabrication arts and incorporated herein by reference, are plasma deposition and physical vapor deposition which are utilized to impart a metal layer onto the stent pattern.

5 The present invention consists of a stent made of a bulk material having controlled heterogeneities on the luminal surface thereof. Heterogeneities are controlled by fabricating the bulk material of the stent to have defined grain sizes which yield areas or sites along the surface of the stent having optimal protein binding capability. The characteristically desirable properties of the inventive stent are: (a) optimum mechanical properties consistent with or exceeding regulatory approval criteria, (b) minimization of defects, such as cracking or pin hole defects, (c) 10 a fatigue life of 400 MM cycles as measured by simulated accelerated testing, (d) corrosion resistance, (e) biocompatibility without having biologically significant impurities in the material, (f) a substantially non-frictional abluminal surface to facilitate atraumatic vascular crossing and tracking and compatible with transcatheter techniques for stent introduction, (g) radiopaque at selected sites and MRI compatible, (h) have an luminal surface which is optimized for surface energy and microtopography, (i) minimal manufacturing and material cost consistent with 15 achieving the desired material properties, and (j) high process yields.

In accordance with the present invention, the foregoing properties are achieved by fabricating a stent by the same metal deposition methodologies as are used and standard in the microelectronics and nano-fabrication vacuum coating arts, and which are hereby incorporated 20 by reference. In accordance with the present invention, the preferred deposition methodologies include ion-beam assisted evaporative deposition and sputtering techniques. In ion beam-assisted evaporative deposition it is preferable to employ dual and simultaneous thermal electron

beam evaporation with simultaneous ion bombardment of the substrate using an inert gas, such as argon, xenon, nitrogen or neon. Bombardment with an inert gas, such as argon ions serves to reduce void content by increasing the atomic packing density in the deposited material during deposition. The reduced void content in the deposited material allows the mechanical properties of that deposited material to be similar to the bulk material properties. Deposition rates up to 20 nm/sec are achievable using ion beam-assisted evaporative deposition techniques.

When sputtering techniques are employed, a 200 micron thick stainless steel film may be deposited within about four hours of deposition time. With the sputtering technique, it is preferable to employ a cylindrical sputtering target, a single circumferential source which concentrically surrounds the substrate which is held in a coaxial position within the source. Alternate deposition processes which may be employed to form the stent in accordance with the present invention are cathodic arc, laser ablation, and direct ion beam deposition. When employing vacuum deposition methodologies, the crystalline structure of the deposited film affects the mechanical properties of the deposited film. These mechanical properties of the deposited film may be modified by post-process treatment, such as by, for example, annealing, high pressure treatment or gas quenching.

Materials to make the inventive stents are chosen for their biocompatibility, mechanical properties, *i.e.*, tensile strength, yield strength, and their ease of deposition include the following: elemental titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, neobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, and stainless steel.

During deposition, the chamber pressure, the deposition pressure and the partial pressure of the process gases are controlled to optimize deposition of the desired species onto the substrate. As is known in the microelectronic fabrication, nano-fabrication and vacuum coating arts, both the reactive and non-reactive gases are controlled and the inert or non-reactive gaseous species introduced into the deposition chamber are typically argon and nitrogen. The substrate may be either stationary or moveable, either rotated about its longitudinal axis, or moved in an X-Y plane within the reactor to facilitate deposition or patterning of the deposited material onto the substrate. The deposited material may be deposited either as a uniform solid film onto the substrate, or patterned by (a) imparting either a positive or negative pattern onto the substrate, such as by etching or photolithography techniques applied to the substrate surface to create a positive or negative image of the desired pattern or (b) using a mask or set of masks which are either stationary or moveable relative to the substrate to define the pattern applied to the substrate. Patterning may be employed to achieve complex finished geometries of the resultant stent, both in the context of spatial orientation of the pattern as well as the material thickness at different regions of the deposited film, such as by varying the wall thickness of the material over its length to thicken sections at proximal and distal ends of the stent to prevent flaring of the stent ends upon radial expansion of the stent.

The stent may be removed from the substrate after stent formation by any of a variety of methods. For example, the substrate may be removed by chemical means, such as etching or dissolution, by ablation, by machining or by ultrasonic energy. Alternatively, a sacrificial layer of a material, such as carbon or aluminum, may be deposited intermediate the substrate and the

stent and the sacrificial layer removed by melting, chemical means, ablation, machining or other suitable means to free the stent from the substrate.

The resulting stent may then be subjected to post-deposition processing to modify the crystalline structure, such as by annealing, or to modify the surface topography, such as by etching to affect and control the heterogeneities on the blood flow surface of the stent.

Example 1: Stent Formation By Sputtering

A ceramic cylindrical substrate is introduced into a deposition chamber with capabilities of glow discharge substrate cleaning and sputter deposition of carbon and stainless steel. The deposition chamber is evacuated to a pressure less than or equal to 2×10^{-7} Torr. Pre-cleaning of the substrate is conducted under vacuum by glow discharge. The substrate temperature is controlled to achieve a temperature between about 300 and 1100 degrees Centigrade. A bias voltage between -1000 and +1000 volts is applied to the substrate sufficient to cause energetic species arriving at the surface of the substrate to have a hyperthermal energy between 0.1 eV and about 700 eV, preferably between 5-50 eV. The deposition sources are circumferential and are oriented to deposit from the target circumferentially about the substrate.

During deposition, the deposition pressure is maintained between 0.1 and 10 mTorr. A sacrificial carbon layer of substantially uniform thickness ($\pm 5\%$) between 10 and 500 Angstroms is deposited circumferentially on the substrate. After depositing the carbon layer, a cylindrical film of stainless steel is deposited onto the sacrificial carbon layer on the cylindrical substrate at a deposition rate between about 10 to 100 microns/hour. After formation of the stainless steel film, the substrate is removed from the deposition chamber and heated to volatilize the

intermediate sacrificial carbon layer between the substrate and the film. After removing the carbon intermediate layer, the stainless steel film is removed from the substrate and exhibits material properties similar to the bulk stainless steel target and surface properties characterized by controlled heterogeneities in grain size, material composition and surface topography. A series of patterns are then machined into the resultant stainless steel film to form a stent by electrical discharge machining (EDM) or laser cutting the film.

Example 2: Stent Formation by Sputtering

The same operating conditions are followed as in Example 1, except that the substrate is tubular and selected to have a coefficient of thermal expansion different than that of the resultant stent. No intermediate layer of sacrificial carbon is deposited onto the substrate, and the outer surface of the substrate is etched with a pattern of recesses defining a desired stent pattern. The substrate is mounted onto a rotational jig within the deposition chamber and rotated at a uniform rate during deposition. Tantalum is used as the target material and deposited into the recesses of the substrate from a single stationary source. After deposition, the temperature of the substrate and the deposited stent are controlled to impart diametric differential in the substrate and stent and permit removal of the stent from the substrate.

Example 3: Stent Formation by Ion Beam-assisted Evaporative Deposition

A cylindrical substrate is introduced into a deposition chamber which has capabilities of: substrate rotation and precise positioning, glow discharge substrate cleaning, ion beam-assisted evaporative deposition, and cylindrical magnetron sputtering. The deposition sources are (a)

dual electron beam evaporative sources placed adjacent one another at the base of the deposition chamber at a fixed distance from the substrate, these are used with simultaneous argon ion impingement onto the substrate from a controlled ion beam source, and (b) a cylindrical magnetron sputtering source with a carbon target capable of circumferentially coating a carbon sacrificial layer of substantially uniform thickness of between 10 and 200 Angstroms onto the substrate.

The substrate temperature is controlled to achieve a substrate temperature between about 300 and 1100 degrees Centigrade. The deposition chamber is evacuated to a pressure less than or equal to 2×10^{-7} Torr. A pre-cleaning of the substrate is conducted under vacuum by glow discharge. The substrate is rotated to ensure uniform cleaning and subsequent uniform deposition thickness. After cleaning the substrate is moved into the magnetron and coated with the carbon layer. The substrate is then moved into position to receive the stent-forming metal coating with simultaneous ion bombardment. One electron beam evaporation source contains titanium while the other source contains nickel. The evaporation rates of each of the titanium and nickel evaporation sources are separately controlled to form a nitinol alloy on the substrate as the stent-forming metal.

Example 4: Planar Deposition of Stent.

The same operating conditions of Example 3 are followed, except that a planar substrate is used. The deposition source is a single electron beam evaporation source containing platinum and is used with simultaneous argon ion impingement onto the substrate from a controlled ion beam source.

The substrate temperature is controlled to achieve a substrate temperature between about 300 and 1100 degrees Centigrade. The deposition chamber is evacuated to a pressure less than or equal to 2×10^{-7} Torr. A pre-cleaning of the substrate is conducted under vacuum by glow discharge. After cleaning the substrate is moved into position within the deposition chamber and coated with platinum from the electron beam evaporation source with simultaneous argon ion bombardment, with the electron beam evaporation source passing platinum through a pattern mask corresponding to a stent pattern which is interposed between the source and the substrate to pass a pattern of platinum onto the substrate.

After deposition, the patterned stent is removed from the substrate and rolled about a forming substrate to a cylindrical shape and opposing ends of the planar stent material are brought into juxtaposition with one another and may be attached by laser welding or left uncoupled.

While the invention has been described with reference to its preferred embodiments, those of ordinary skill in the relevant arts will understand and appreciate that the present invention is not limited to the recited preferred embodiments, but that various modifications in material selection, deposition methodology, manner of controlling the material heterogeneities of the deposited stent material, and deposition process parameters may be employed without departing from the invention, which is to be limited only by the claims appended hereto.